Therapeutic Strategies for Localized Prostate Cancer

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Prostate-specific antigen determinations for prostate cancer screening have led to a dramatic increase in the number of men who are diagnosed with organ-confined and therefore potentially curable prostate cancer. Advances in predicting outcomes with artificial neural networks may help to recommend one therapy over another. Less invasive forms of treatment, such as high-intensity focused ultrasound, may ultimately give patients additional options for treatment. Furthermore, attempts to better define the role of both neoadjuvant hormonal therapy and chemotherapy may give higher-risk patients better outcomes than with current treatments. These advances as well as continued research will likely lead to a day when more and more men with organ-confined disease will be cured. [Rev Urol. *2001;3(suppl 2):S39–S48*]

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Clearly the increased use of prostate-specific antigen (PSA) by urologists and internists alike has led to the dramatic rise in the number of men diagnosed with organ-confined cancer of the prostate. The vast majority of these patients have no symptoms of their disease and have unremarkable prostate glands on digital rectal exam. Curative therapy, either in the form of radical prostatectomy or radiation therapy, is an option for many of these patients, given their ages and health. Pathological examination of excised

prostate specimens from patients who have Gleason scores less than 6 and serum PSA levels of <10 ng/mL has demonstrated a high incidence of organ-confined disease, thus improving the possibility of a cure. Advances in the surgical, radiotherapeutic, and chemotherapeutic management of these patients have improved treatment-related morbidity and may augment the success of currently established treatment options.

Artificial Neural Networks in the Diagnosis of Prostate Cancer

Clinical diagnosis and treatment planning require analysis of multiple clinical data to arrive at appropriate patient management decisions. These decisions often incorporate an individual clinician's experience, and the relevant literature regarding the significance of individual clinical variables. In addition, the clinician may also be aided by statistical modeling that allows clinical predictions to be derived from data stored in large institutional databases. Established statistical methods, such as logistic regression, have typically been used to derive these models, and this approach has been validated in clinical practice.[1] However, the task of deriving valid models becomes more complex as the number of included variables increases, and more powerful methods of modeling are being developed.[2] One such method is broadly referred to as artificial neural network (ANN) modeling.

An artificial neural network is a mathematical model that assumes a mathematical relationship between any number of input parameters (ie, clinical variables) and an outcome of interest (eg, the risk of prostate cancer metastasis, 5-year survival, etc.).[3] ANNs were inspired by the complex interconnections of biological nervous systems but, in reality, the similarity between the two is merely schematic.

The utility of ANNs in medical applications has been explored for more than a decade.[4] ANNs have been proposed for image analysis applications, such as reading Pap smears, analyzing electrocardiogram tracings, and interpreting chest radiographs. Neural networks have also been widely explored in the area of prostate cancer management. Snow and co-workers published a pilot study in which ANNs were used to predict the outcome of first biopsy on the basis of PSA, digital rectal exam, and transrectal ultrasound (TRUS). Tewari and colleagues have used ANNs to predict stage,[5] and other investigators have applied ANNs to predict cancer recurrence.[6,7]

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Despite the fact that ANN modeling has been shown to work, it has not fulfilled the expectation of some proponents that it would eclipse more conventional statistical techniques. There are several reasons for this. Training a neural network requires a relatively large amount of data. One of the strengths of neural network modeling is that it is largely independent of assumptions regarding the statistical distributions and relationships contained in the training data. Although this may result in a more precise model given a sufficiently large training set, the resulting model tends to be more data intensive.

Although several studies have suggested that ANNs can give more accurate clinical predictions than linear regression models, it remains to be demonstrated that this improvement in performance is clinically significant. Another purported advantage of ANNs is that they can inherently detect and incorporate nonlinear relationships between input variables. This may prove to be a significant advantage in the future, as genetic information becomes more widely available and as new disease markers are identified and made available. To date, however, the nonlinear modeling ability of ANNs has not clearly conferred an advantage.

The role of ANNs as decision aids has not been clearly defined. A neural network model simulates statistical relationships contained within the training data. The ANN is limited to information contained within the input variables, but a single clinical decision may depend on many factors not included in the ANN. Neural networks have no common sense, compassion, or creativity. They have no intuition and no foresight. They can only give estimates of risk; they cannot make decisions. Furthermore, ANNs are limited to patient populations that are similar to the training set. In general, ANNs are better at interpolating than extrapolating. An ANN can make valid estimates for a patient population no more diverse than that upon which it was trained.

The Complete Prostatectomy

Radical retropubic prostatectomy remains a time-honored therapy for locally confined prostate cancer. Although the retropubic approach to simple prostatectomy was first described by Millin in 1947, it was not widely accepted for radical

prostatectomy because of high morbidity and mortality rates.[8] The anatomic retropubic radical prostatectomy evolved from a succession of anatomic dissections and diminished complication rates. A modification of Campbell's technique of radical prostatectomy has been performed at the University of Colorado Health Sciences Center.[9,10] The technique emphasizes dissection of the prostate from the base to the apex. Removal of all malignant tissues with acceptable tumor-free margins and tissue dissection performed in the proper sequence to minimize iatrogenic, lymphatic, and hematogenous dissemination are provided with this technique. A new device called the LigaSure® vessel sealing system has been used to modify the technique of retropubic antegrade radical prostatectomy.

Because the [LigaSure vessel sealing] system uses the body's own collagen to reform the tissue, it resists dislodgment and leaves no foreign material behind.

The LigaSure device is used during several phases of the antegrade radical prostatectomy. When the bladder neck is divided from the prostate, the laparoscopic LigaSure device is used to dissect and seal the tissue between the bladder neck and prostate. During the second phase of this technique, the LigaSure device is applied to seal and divide the vasa and the vessels supplying the seminal vesicles. The device is used next after the lateral pedicles are identified in order to seal, dissect, and divide them. Lastly, the endopelvic fascia, which remains toward the apex, is dissected and sealed with the LigaSure device. The dorsal vein complex also is directly sealed with the LigaSure device in the majority of cases.

At the University of Colorado Health Sciences Center (UCHSC), the modification of the antegrade radical prostatectomy using the laparoscopic LigaSure device was carried out in 35 patients (Group 1), whereas the conventional approach was performed in 31 patients (Group 2). There was no difference between the two groups in terms of mean age, preoperative PSA level, biopsy, and radical prostatectomy Gleason scores. Comparison of the modified technique with the conventional approach was performed in terms of mean operative time, blood loss, hospital stay, and catheter removal. Mean operative time, blood loss, and hospital stay were lower in Group 1 than in Group 2. None of the 66 patients required any blood transfusions. Urethral catheter was removed in 2 weeks in both techniques. Early postoperative complications, such as fever (n = 2), penile edema (n = 1), and hematuria (n = 1) were mild and well tolerated in both groups.

The LigaSure vessel sealing system works by applying a precise amount of bipolar energy and pressure to denature the elastin and collagen in vessel walls, resulting in permanent occlusion. Because the system uses the body's own collagen to reform the tissue, it resists dislodgment and leaves no foreign material behind.

The clinical results at UCHSC demonstrate that mean operative time, blood loss, and hospital stay were lower when using the modified technique rather than the conventional approach. Shorter operative time offers a potential advantage in terms of cardiac and pulmonary morbidity, especially in elderly patients. Although blood loss between the two groups was statistically significant ($P < .05$), it may be clinically insignificant in this series, because none of the 66 patients required blood transfusion. A comparison of the incontinence and impotence rates was not performed in this series, because it is too early to assess the impotence and incontinence rates, given that it has been less than a year from the surgery for most of the patients. It is felt, however, that the phases of the operation, which might effect the incontinence and impotence rates, are similar in both techniques.

Erectile Dysfunction: What the Patient Needs to Know About Impotence and Prostate Cancer

The most common adverse consequence of prostate cancer and its treatment is the development of erectile dysfunction (ED). Regardless of the treatment chosen—radical prostatectomy (RP), radiation therapy (RT), watchful waiting, cryotherapy, hormones—ED occurs in most patients. For example, Lubeck et al compared sexual function at 2 years after RP, RT, hormonal therapy, and observation and found no differences with only 24.8% to 29.1% in the various groups reporting good function.[11] McCammon and associates reported similar levels of sexual function after RP and RT with only 11.1% to 12.2% describing normal erections.[12] Despite these low figures for preservation of erectile function, the majority of men do not seek treatment and/or many urologists do not encourage it to a successful outcome.

Following RP, ED is almost universal initially. Recovery of function after nerve-sparing RP rarely occurs by 6 months, and it may take up to 12 to 18 months. Etiology of ED is neurogenic at first, but then vascular factors develop, making treatments less successful even if nerve function returns. Early treatment of ED seems to improve ultimate recovery and response to therapy. Montorsi et al

demonstrated that early use of intracavernosal therapy with PGE-I resulted in greater return of function compared to those with no therapy.[13]

Although Walsh and Catalona have reported preservation of erectile function in most men undergoing nerve-sparing RP,[14,15] most other authors describe ED in more than 70%. For example, the group from Stanford reported only 31.9% potency after bilateral nerve-sparing, but only 15.9% described "good erections,"[16] and Talcott and associates report that 79% have "inadequate erections."[17] Of 93 men undergoing nerve-sparing RP, only 9% were able to have a "full erection" and 38% "partial erection."[18] Therefore, despite nerve-sparing RP, ED is very common, and it is nearly universal in the unilateral or non–nerve-sparing procedures performed by many urologists.

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Sildenafil (Viagra) has become the first choice for most men, but it requires an intact neurologic supply, not usually present in the first 6–12 months after RP. There is now sufficient experience with Viagra to conclude that it is rarely successful unless bilateral nerve-sparing has been performed. Following a bilateral procedure, Lowentritt et al reported improved erections in 53% and improved ability to have intercourse in 40%.[19] However, mean scores for erectile function were still quite low at 14 out of a maximum of 30. Zippe and associates reported an 80% success with Viagra (defined as achievement of vaginal intercourse) in those having bilateral nerve-sparing compared to no success with unilateral or non–nerve-sparing. It is not reported how many men had rigid or normal erections after Viagra, but patient and partner satisfaction was very high.[20] Hong et al recently described their experience with Viagra after nerve-sparing RP.[21] Between 0 and 6 months after surgery, treatment satisfaction was 26%, peaking at 60% between 18 and 24 months. The consensus of studies is that Viagra is reasonably successful in men undergoing bilateral nerve-sparing RP, but not if one or both nerves are sacrificed and that it is rarely successful in the first 6 months after surgery. Because early treatment of ED is recommended and many men wish to resume sexual activity, intracavernosal therapy should be encouraged.

In an attempt to enhance recovery of erections and, perhaps, response to Viagra, urologists have studied the use of intraoperative cavernous nerve stimulation and salvage.[22,23] Results are inconclusive at this time. Other urologists have evaluated the use of sural nerve interposition in place of resected cavernous nerves at the time of RP in 12 men.[24] Overall, 7 out of 12 men have convincing return of erectile function at 1-year follow-up, although only 4 out of 12 men can have vaginal penetration, and fewer have normal rigidity.

The treatment that has the highest patient and partner satisfaction and that provides the best rigidity and spontaneity is placement of an inflatable penile prosthesis (IPP).[25] Men who fail or dislike intracavernosal or Viagra therapy should be offered IPP. Placement of an IPP usually is not more difficult after RP. If men have ED before RP (and have failed medical therapy) or would prefer IPP as a urologist is finishing RP, the reservoir can be placed under the rectus muscle and connected to the scrotal pump. The cylinder tubing can be connected to itself, and later the cylinders can be placed transscrotally and the connections made. This staged approach may be less morbid, allow easy reservoir and pump placement, and avoid possible post-RP infection of the corpus cavernosa.

Recently, Morgentaler and DeWolf described immediate simultaneous IPP placement after the end of RP in 100 patients.[26] No prosthetic infections occurred, eight patients required reoperation for device failure (n = 3) and for curvature (n = 5) related to Foley catheter positioning, and most were using their IPP at 3 months after RP. Because many men with ED after RP failed to respond to medical therapy and are reluctant to undergo another operative procedure to correct the quality of life problem, simultaneous IPP placement at the end of RP may be beneficial. Regardless of when IPP is placed, urologists should be more assertive about offering this treatment to their prostate cancer patients with ED.

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High-Intensity Focused Ultrasound for Prostate Cancer

High-intensity focused ultrasound (HIFU) is generated by a high-power acoustic transducer that produces focused ultrasound waves to generate

extremely high temperatures within a very small, precisely defined volume. Because of the temperatures obtained, tissues are destroyed at the target site without damage to any intervening structure. Necrosis followed by cystic areas is noted at the target area. The frequency range for the piezoelectric transducers can vary from 0.5 to 10 MHz.

Overall, the [high-intensity focused ultrasound] procedure has been tolerated well with promising results.

The ideal HIFU system consists of a variable focus, must have a stable position during firing, have on-line imaging, be simple to handle, have a short treatment time and compact probe design, and require minimal anesthesia. The current devices consist of a treatment table, motor driven applicator, ultrasound transducer, rectal wall distance control unit, piezoelectric ceramic transducer, and cooling pump for the rectal balloon. The rectal wall distance control unit and cooling pump were added as extra safety features.

Two large series of patients from Europe were recently reported in the literature. Gelet et al performed HIFU treatment on 82 patients with stage T1–T2 prostate cancer who were not candidates for radical prostatectomy.[27] The disease-free survival rate in patients with a PSA < 15 ng/mL, a Gleason sum < 8, a prostate volume < 40 cm^3, and the number of positive biopsies < 5 was 68% at 60 months. Patients with PSA levels < 10 ng/mL and Gleason scores < 7 were considered to be at low risk. This group had a disease-free survival rate of 83% at 60 months. One patient developed a recto-urethral fistula that was managed with Foley catheter drainage for 6 weeks. Two (4%) patients had total incontinence, and another 11 (13%) reported stress incontinence. Potency was preserved in 8 of 35 previously potent patients. Five patients (6%) required a transurethral resection of the prostate (TURP) for urinary retention. Finally, 14 (17%) patients developed urethral strictures that were managed endoscopically.

Chaussy and Thuroff found an 80% cancer-free rate on follow-up sextant biopsy after treating 184 patients with HIFU.[28] Patients included in their study were unsuitable for surgery and had stage T1–T2 prostate cancer. The mean follow-up was 193 days with a range of 0 to 903 days. Ninety-seven percent of patients had a PSA nadir of <4 ng/mL, whereas 61% had a PSA nadir of <0.5 ng/mL. The incidence of rectal burns decreased from 15% to 0.7%, and the incidence of recto-urethral fistulas dropped to 0.5% from 3.1% when the transducer frequency was increased from 2.25 to 3.00 MHz. One third of all patients required a subsequent TURP within 6 to 8 weeks of their procedures. The post-treatment potency rate was 33%. Stress incontinence rates decreased from 24% to 4% when an apical safety margin of 5 mm was added to the treatment protocol. Importantly, this modification in protocol did not lead to an increase in residual apical cancer.

In the United States, the Ablatherm (Edap Technomed, Norcross, GA) HIFU is currently being investigated as a means for treating patients with locally recurrent prostate cancer after having failed external beam radiation therapy. The multicenter trial is being conducted at Georgetown University Hospital, Baylor College of Medicine, and the University of California at San Francisco. To date, 22 patients have been treated with an average follow-up of 11 months (range, 14 days to 12 months). At 3 months, 14 of 20 patients had PSA levels that were <1.0 ng/mL. At 6 months, 9 of 14 patients had PSA levels < 1.0 ng/mL, and 11 of 14 patients had negative biopsies. PSA levels were <1.0 ng/mL for 5 of 8 patients at 12 months. In addition, biopsy results at 12 months were negative in 7 out of 8 patients. Generally, nonresponders had Gleason scores > 8 with pretreatment PSA levels > 10 ng/mL. Urinary retention, the most common adverse event, occurred in 64% of patients. Five of these patients required transurethral resection of obstructing necrotic tissue. Fifty percent of patients developed lower urinary tract infections; the percentage of those affected by stress or urge incontinence was 36% and 9%, respectively. In addition, the rate of urethral stricture was 9%. Overall, the procedure has been tolerated well with promising results. As the power of the study increases and as the period of follow-up lengthens, the ultimate role of HIFU in the treatment of recurrent prostate cancer will be better defined.

Chemotherapy for Early Prostate Cancer

Traditionally, chemotherapy for prostate cancer was perceived to be ineffective and was reserved only for those patients who had symptomatic hormone-refractory disease. Indeed, previous reviews have confirmed this premise. A review by Yagoda and Petrylak of 26 chemotherapy studies performed in men with hormone-refractory prostate cancer between 1988 and 1991 demonstrated a disappointing overall response rate of only 8.7% (95% confidence intervals = 6.4% to 9.0%), without a trend toward improvement in survival.[29]

However, more recent studies have demonstrated significant anti-tumor activity, as measured by palliation of bone pain, declines in serum PSA, as well as reduction in soft tissue masses. The approval of the combination of mitoxantrone and a corticosteroid for the palliation of bone pain in patients with hormone-refractory prostate cancer was the first step in shifting the paradigm of chemotherapy in prostate cancer. Other combinations, such as estramustine plus taxanes, estramustine plus vinblastine, or estramustine plus VP-16 have also demonstrated significant anti-tumor activity.[30] However, complete responses are rare when these regimens are administered to advanced patients. Perhaps one reason for the failure of chemotherapy to prolong survival in prostate cancer patients is that these men are treated too late in the course of their disease. In breast and colon cancer, chemotherapeutic agents administered to patients with metastatic disease will improve survival minimally, or not at all. Yet, when these drugs are administered to high-risk colon and breast cancer patients in the adjuvant setting, clear survival differences are observed. Investigators are now evaluating the role of administering chemotherapy to high-risk prostate cancer patients in conjunction with definitive local therapy.

The approval of the combination of mitoxantrone and a corticosteroid for the palliation of bone pain in patients with hormone-refractory prostate cancer was the first step in shifting the paradigm of chemotherapy in prostate cancer.

Current trials evaluating chemotherapy in early disease: Neoadjuvant therapy. Two regimens known to have activity in advanced-disease patients have been evaluated in high-risk men prior to radical prostatectomy. Pettaway et al administered a regimen that alternated the combination of ketoconazole and adriamycin with vinblastine and estramustine in 30 patients,[31] and Clark et al administered oral estramustine/VP-16 to 18 patients.[32] Both regimens are estramustine-based, which can affect androgen ablation and thus can make it difficult to differentiate the effect of chemotherapy from hormonal therapy. The results in two small, phase two studies appear similar, with the rates of organ-confined disease post-chemotherapy/prostatectomy ranging between 33% and 31%.[33] Most disappointingly, neither study was able to demonstrate a complete pathological response, despite normalizaton of PSA in 50% of patients.

Studies have also evaluated the combination of estramustine and vinblastine concomitantly with radiation therapy. Zelefsky et al administered three 8-week cycles of estramustine and vinblastine combined with high-dose conformal three-dimensional external beam radiation therapy (65–70 cGy) to high-risk prostate cancer patients. The 2-year PSA relapse-free survival rate was 60%, with acceptable rates of genitourinary and gastrointestinal toxicity.[34] Thus, combined RT/chemotherapy seems to be a safe and effective treatment strategy for evaluation in future phase III trials.

Adjuvant therapy. Although mitoxantrone combined with a corticosteroid is effective in palliating patients with metastatic prostate cancer, no survival advantage can be detected when mitoxantrone is compared to corticosteriods alone. Ninety-six locally advanced or metastatic patients were randomized to receive combined androgen blockade alone or in combination with mitoxantrone. The most striking difference in survival was seen in those patients with locally advanced disease, with those patients receiving mitoxantrone achieving a median survival of 80 months versus those treated with androgen blockade alone surviving a median of 36 months. Although these results are impressive, further confirmation in larger studies is necessary. The Southwest Oncology Group and Cancer and Leukemia Group B are collaborating on a study that will compare 2 years of adjuvant hormone therapy plus six cycles of mitoxantrone chemotherapy to androgen blockade in patients post–radical prostatectomy. The study is designed to detect a 30% increase in survival at 10 to 13 years. Of note, early chemotherapy was not found to prolong survival in the Wang trial in patients with established metastatic disease.[35]

In conclusion, phase II studies have demonstrated promising efficacy of early chemotherapy. However, such treatments can only be considered investigational, and the role of early chemotherapy can only be defined in the future through large randomized clinical trials.

Neoadjuvant Hormonal Therapy for Prostate Cancer: Does It Work?

Many patients with localized prostate cancer treated with curative intent will progress over time. Stratifying patients into risk categories at the time of diagnosis may allow patients to be treated based on their likelihood of progression following therapy, with low-risk patients usually doing well with

Table 1
Summary of 7 Current Prospective Neoadjuvant Hormonal Therapy (NHT) Trials Using Short-Term NHT

Investigator	Sample Size	Clinical Stage	Type of NHT	Change in Serum PSA	Positive 3-Year Margin Rate	PSA Recurrence
Labrie, 1994[59]	161	T2/T3	3-month L+F	N/A	8% vs 34%	
Soloway, 1995[44]	303	T2b	3-month L+F	14.3 to <.5 µg/L in 70%	18% vs 48%	28% vs 26%
VanPoppel, 1995[49]	130	T2b/T3	6-week EP	14 to 1.0 µg/L	20% vs 46%	
Goldenberg, 1996[50]	213	T1/T2	3-month CPA	13 to 1.1 µg/L	28% vs 65%	30% vs 28%
Fair, 1997[51]	148	T1/T2	3-month CPA	8.9 to 0.2 µg/L	18% vs 37%	
Witjes, 1997[52]	354	T2/T3	3-month G+F	20 to 0.8 µg/L	27% vs 46%	
Hugosson, 1996[53]	111	T1-T3a	3-month	N/A	23% vs 41%	

L+F, leuprolide acetate + flutamide; EP, estramustine phosphate; CPA, cyproterone acetate; G+F, goserelin + flutamide.

monotherapy and high-risk patients usually having a high likelihood of failure and ultimately dying of prostate cancer. Although the pool of patients presenting with early prostate cancer is increasing, there remains a significant number of men who are diagnosed with adverse prognostic features and hence a higher likelihood of progression if treated with standard therapies. These patients may benefit from multi-modality therapy. Neoadjuvant hormonal therapy (NHT) is one potential multi-modality strategy to improve long-term disease control in high-risk prostate cancer.

Mechanism of action of NHT. Potent and reversible agents for androgen ablation therapy provide an acceptable method for inducing tumor regression prior to radical prostatectomy or radiation therapy. Prostate tumor cell death, not just tumor shrinkage, occurs following androgen withdrawal.[36–38] Monitoring of changes in PSA during NHT helps to confirm response and identify those not responding appropriately. Maximal tumor regression is likely achieved when PSA reaches its nadir level. Prostate cancer is composed of a mixture of cells that are androgen hypersensitive and some that are less sensitive.[39] The goal of NHT therefore is to eliminate the cells responsible for local extension or invasion and leave the remaining less sensitive cells to be removed via surgery or radiation.

Neoadjuvant hormonal therapy is one potential multi-modality strategy to improve long-term disease control in high-risk prostate cancer.

Advantages and disadvantages of NHT. The potential advantages of NHT (luteinizing hormone-reducing hormone [LHRH] analogue ± anti-androgen) are numerous. All studies have shown significant prostate downsizing, with prostate volume decreasing approximately 30% to 35%. Some authors have reported decreased operative time and blood loss,[40,41] whereas others have found no significant difference in regards to operative time and blood loss.[42–44] Shrinkage of the glands in the prostatic capsule might theoretically improve surgical planes. Gomella demonstrated that patients treated with NHT achieve complete continence 3 weeks earlier than patients who did not receive NHT, most probably explained by improved apical dissection induced by apical prostatic involution.[45]

NHT also has potential disadvantages. Androgen blockade causes decreased libido and potency, gynecomastia, and hot flashes, with antiandrogens having their own

unique side effect profiles.[43,46] Concerns over osteoporosis and loss of muscle mass have also been raised. Most side effects are reversible after cessation of treatment. In some studies, prostatectomy has been noted to be more difficult, owing to a desmoplastic reaction in the tissues, especially surrounding the posterior dissection.[47] The concern that androgen-resistant clones might develop is highly unlikely.

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Another difficulty is the fact that prostate pathology is significantly altered by the NHT.[48] The changes induced are so extensive with 3 months of NHT that standard Gleason scores should not be applied to these radical specimens.

Neoadjuvant therapy and radical prostatectomy. Two consistent findings are apparent in contemporary NHT series. Prostate volume by TRUS was found to decrease by 30% to 50%, and PSA levels reliably decreased to approximately 95% of pretreatment values. The majority of current studies also conclude that the percent change in PSA or PSA absolute value after NHT was not predictive of final pathological stage.

Seven contemporary randomized, controlled studies have been reported (Table 1). The notable U.S. Multi-Institutional study by Soloway found a decrease in positive margins from 47% to 17%. Only PSA level and pre-radical prostatectomy androgen deprivation had a significant impact on margin positivity. Several other studies have demonstrated similar findings of decreased positive margins.[49-53]

Concern that the clinical changes are artifactual seems unlikely because several lines of evidence suggest that the NHT-induced decrease in positive margin rates is a real, rather than an artifactual, phenomenon. Most importantly, all randomized studies that used a single central and experienced pathologist report similar (50%) decreases in positive margin rates.[44,50,51]

Gomella et al reported early long-term PSA follow-up data using NHT. The nonrandomized study demonstrated that for clinical T3 disease, 4 months of NHT can improve the margin positivity rate to 48%.[54] However, by 3 years, 75% of patients had progression. Data on the long-term PSA-based follow-up in patients with clinical stage T2 has now been published by Goldenberg and Soloway and suggests similar PSA recurrence rates in both arms.[55,56]

Long-term NHT prior to radical prostatectomy. Although most studies have chosen 3 months as the duration of androgen deprivation, recent publications have suggested this interval is too short.[47] In a preliminary group of patients treated for 8 months prior to prostatectomy, Gleave and associates demonstrated that the PSA nadir was reached in 14% of patients at 3 months, in 40% at 5 months, and in 84% at 8 months.[57] Furthermore, the positive margin rate was only 5% after 8 months of NHT. The Canadian Urologic Oncology Group (CUOG) study will address the issue of 3 versus 8 months of NHT before radical prostatectomy.[58]

Main Points

- Despite the fact that artificial neural network modeling has been shown to work, it has not fulfilled the expectation of some proponents that it would eclipse more conventional statistical techniques.
- A new device (called the LigaSure® vessel sealing system) has been used to modify the technique of retropubic antegrade radical prostatectomy; a study at the University of Colorado Health Sciences Center showed that mean operative time, blood loss, and hospital stay were lower for patients with whom the device was used compared to the conventional approach.
- There is now sufficient experience with Viagra to conclude that it is rarely successful after radical prostatectomy unless bilateral nerve-sparing has been performed; the treatment for erectile dysfunction that has the highest patient and partner satisfaction and that provides the best rigidity and spontaneity is placement of an inflatable penile prosthesis.
- European trials using high-intensity focused ultrasound (HIFU) were recently reported. Disease-free survival rate in patients with PSA < 15 ng/mL was 68% at 60 months; in low-risk patients the rate was 83% at 60 months. A U.S.-based multicenter trial of HIFU is currently under way.
- Phase II studies have demonstrated promising efficacy of early chemotherapy; however, such treatments can only be considered investigational, and the role of early chemotherapy can only be defined in the future through large randomized clinical trials.
- There is extensive data to indicate that neoadjuvant hormonal therapy (NHT) may have a role in the management of patients with prostate cancer. Concerning radical prostatectomy, most data at present concerns the use of 3-month NHT; however, a major trial from the Canadian Urologic Oncology Group comparing 3 versus 8 months of NHT is currently in its follow-up phase.

Neoadjuvant hormonal therapy combined with radiation therapy. The use of NHT with radiotherapy for prostate cancer is far less controversial than the surgical use of NHT. The Radiation Therapy Oncology Group has prioritized the study of NHT with radiotherapy, and most new prostate cancer studies include some form of NHT.

In summary, there is extensive data to indicate that neoadjuvant hormonal therapy may have a role in the management of patients with prostate cancer. Concerning radical prostatectomy, most data at present concerns the use of 3-month NHT. Preliminary long-term NHT trials are showing improved short-term disease control with a very low positive margin rate. However, a major trial from CUOG comparing 3 versus 8 months of NHT is currently in its follow-up phase. ■

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